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PROTON THERAPY SPECIAL FEATURE: REVIEW ARTICLE

Neutron dose and its measurement in proton therapy—current State of Knowledge

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ABSTRACT

Proton therapy has shown dosimetric advantages over conventional radiation therapy using photons. Although the integral dose for patients treated with proton therapy is low, concerns were raised about late effects like secondary cancer caused by dose depositions far away from the treated area. This is especially true for neutrons and therefore the stray dose contribution from neutrons in proton therapy is still being investigated. The higher biological effectiveness of neutrons compared to photons is the main cause of these concerns. The gold-standard in neutron dosimetry is measurements, but performing neutron measurements is challenging. Different approaches have been taken to overcome these difficulties, for instance with newly developed neutron detectors. Monte Carlo simulations is another common technique to assess the dose from secondary neutrons. Measurements and simulations are used to develop analytical models for fast neutron dose estimations. This article tries to summarize the developments in the different aspects of neutron dose in proton therapy since 2017. In general, low neutron doses have been reported, especially in active proton therapy. Although the published biological effectiveness of neutrons relative to photons regarding cancer induction is higher, it is unlikely that the neutron dose has a large impact on the second cancer risk of proton therapy patients.

INTRODUCTION

Proton therapy has become a well-established cancer treatment modality in radiation oncology.[1] It has shown dosimetric advantages over conventional radiation therapy using photons for many treatment sites.[2] Despite the high investment cost to establish a new proton therapy facility, the number of proton therapy centers worldwide has been increasing considerably. This development has given a lot more patients access to proton therapy. But it is still important to carefully select the patients who benefit the most from the advantages of proton therapy. For instance, the precision of proton irradiations combined with the accuracy and reproducibility of positioning and immobilization of head and neck patients, has made lesions inside the head a very important indication for protons. On the other hand, one of the main advantages of clinical proton irradiations is the possibility to conform the deposited dose to the target volume. Thanks to the finite range of protons and the low entrance dose proximal to the target volume, the irradiated volume[3] and the integral dose can be considerably smaller than in photon radiation therapy. This has been shown in many treatment planning studies and confirmed by different measurements.[2] One patient cohort which clearly can benefit from this are pediatric patients. Not only are most of the structures to be irradiated smaller than in adult patients and therefore the distances to organs at risk smaller, they are also at higher risk to develop late effects because of their long life expectancy and therefore a smaller integral dose is clearly beneficial for them. One of the possible late effects in pediatric radiation oncology is the risk of radiation induced second primary cancers. This is equally important in proton and in photon radiation therapy. A smaller irradiated volume and a lower integral dose in proton *vs* photon radiation therapy would directly imply a lower risk of late effects for protons. Unfortunately, it is not as straight forward, as in both cases we are dealing with a mixed radiation field of different particles and energy spectra. Concerning late effects, beside the lower integral dose in proton therapy, the main difference is in the production of secondary neutrons. In proton therapy, secondary neutrons are mainly produced by interactions of protons in the therapy beam with the treatment delivery system and the patient. The dose deposited by protons and secondary charged particles is limited around the target volume, whereas secondary neutrons scatter further away and lead to a whole body neutron dose exposure. This dose is not part of the therapeutic dose and therefore is of direct importance for the induction of late effects. On the other

hand for photon irradiations, neutrons are only produced in a considerable amount above an energy threshold. Only photon beams with a nominal energy of more than 10 MeV produce a considerable number of neutrons. Therefore, the neutron dose from many of the clinically used photon treatment plans is negligible for neutron induced late effects. In addition, the neutrons in high energy photon beams are mostly produced in the beam delivery system and only very few in the patient. So considering only these aspects, one could imply that the risk for late effects because of secondary neutron dose is lower for photons. These are only two examples that show how careful one must be when comparing the effects of neutrons in proton and photon radiation therapy.

Since the beginning of clinical proton therapy, it has been known that neutrons are produced by interactions of the proton beam with matter. Although difficult to measure, it has been accepted that the absorbed dose for a patient from neutrons in proton therapy is small. The concerns about the neutron exposure arose from the facts, that the whole body of the patient gets irradiated and the biological effectiveness of neutrons is higher compared to photons and electrons. Studies which investigated the neutron biological effectiveness, the neutron radiation quality factor, or neutron radiation weighting factors showed varying results and the errors were big. Therefore, it remained unclear how important the neutron contribution to the risk for late effects for a proton therapy patient actually is. An extensive assessment of neutron dose was presented in 2008 in the article by Xu et al.[4] They wrote a review about dosimetry studies on external-beam radiation treatment with respect to second cancer induction. They say that it was confirmed that there is an increased cancer risk for patients after radiation therapy. Although it was not differentiated between different radiation qualities. They conclude, that 'many of the past dosimetry studies are based on inconsistent and sometimes confusing dose quantities and a systematic dosimetry methodology for quantifying secondary organ absorbed doses needs to be developed in the future'. In addition, they point out that 'the protection quantity, effective dose, should not be used for absolute risk assessment for specific patient or for epidemiological studies. Instead, organ-specific equivalent doses must be used and documented'. They uncovered that some of the most important studies in the past were not able to contribute to the understanding of the dose–response curve, especially for relatively low doses. They conclude that further studies with reporting of organ-specific absorbed doses are necessary, for instance using computational phantoms and Monte Carlo simulations.[4] Later in 2015, Schneider et al[5] published an article that highlights and discusses the controversy about the impact of the neutron dose in proton therapy and what new epidemiological studies have contributed to the understanding. The task group 158 of the American Association of Physicists in Medicine (AAPM) published their findings on measurement and calculation of doses outside the treated volume from external-beam radiation therapy in an article in 2017.[6] In a very systematic way, they present common practices and challenges in the quantification of stray doses in radiation therapy. They start with concerns with respect to non-target radiation such as radiation-induced second cancers. Further, they describe the sources of out-of-field doses and the corresponding dose estimates for different treatment modalities. A lot of details are given about measurement approaches and all current measurement techniques in neutron dosimetry are discussed. Beside computational approaches, also very important key points in dose reporting, especially for neutron doses, are given. In the end, they point out that as cancer treatments using radiation therapy modalities have shown increasing success, the issue of non-target dose has become an important topic to understand.

This article now tries to summarize the developments in the different aspects of neutron dose in proton therapy since 2017. For this review, 28 publications were included and structured into neutron measurements and detectors (16), and neutron dose distributions and their consequences (14), where 2 publications covered topics in both sections.

NEUTRON MEASUREMENTS AND DETECTORS

An important aspect of neutron dosimetry is the choice of the dose quantity. In photon radiation therapy, it is common to report doses in the form of absorbed dose. Measurement devices are calibrated in absorbed dose and no biological weighting is necessary. In proton dosimetry, one has to be more careful, as the biological dose deposition mechanisms are different from photons and electrons. For the prescription of therapeutic doses in clinical proton therapy, it is established to use a constant relative biological effectiveness (RBE) for tumor control of 1.1.[7] Therefore, the absorbed dose from protons is usually weighted by this RBE and given in $Gy_{[RBE]}$ to indicate that the biological effects have been accounted for. This keeps the formalism simple for proton dosimetry, although the RBE in principle is a function of particle type, energy, dose (rate), cell type, and biological endpoint. For neutrons it is more complicated. Many different metrics exist to quantify the neutron dose outside the treated volume. The AAPM task group 158 summarizes the implications of these metrics for neutron dosimetry in their latest report: "Whichever metric is selected, the manner of this conversion should be explicitly stated. The interpretation of results from the literature is sometimes difficult because quantities are not used correctly or in a consistent manner for specific applications. Also problematic is the fact that many biologically weighted dose terms are designed for scenarios in radiation protection, not radiation therapy."[6] According to the International Commission on Radiological Protection, the preferred way to handle high-LET radiation is to use absorbed dose weighted with an RBE for the investigated end point.[8–10] In the case of neutrons this is difficult, as the chosen end point might not have been measured and the reported neutron RBE ranges from less than 1 to over 200.[11] This means that the RBE formalism for reporting neutron dose is currently not practical and therefore the AAPM task group 158 recommends to use radiation protection quantities to report the neutron dose in Sievert.[6] Most recent investigations on out-of-field neutron doses have reported their findings in neutron ambient dose equivalent, especially when measurements were done. Neutron ambient dose equivalent is an operational dose quantity for area monitoring and serves as an estimate of the effective dose of a person standing at the point of interest in the neutron radiation field.[12] Although a neutron

detector can measure a value of neutron ambient dose equivalent in a specific location, the actual measurement value represents a whole body neutron dose. Consequently, one needs to be careful and aware of the limitations when interpreting measurements of neutron ambient dose equivalent as point doses in the context of radiation therapy.

A recent systematic investigation on out-of-field secondary neutron spectrometry and dosimetry using Bonner spheres has been published by Trinkl et al.[13] The neutron dosimetric properties and angular dependency for scanned proton beams of 75, 140, and 200 MeV impinging on a PMMA phantom were compared. Neutron ambient dose equivalent values ranging from 0.3 Sv/Gy (75 MeV; 90°) to 24 μSv/Gy (200 MeV; 0°) were measured at a distance of 2 m from the isocenter. The highest neutron dose was measured downstream behind the phantom. The different Bonner spheres provided the possibility to determine the neutron energy spectrum at each measurement point. With this information they were able to identify an evaporation peak at 0° and 45° in the neutron fluence at around 1 MeV neutron energy. These neutrons contributed about 50% to the total neutron ambient dose equivalent, independent of the proton beam energy.

Working group 9 of the EURADOS project published their work about three-dimensional measurements of neutron and gamma-ray doses in a water phantom with 200 dedicated measurement positions using a variety of passive detectors.[14] They used two types of polyallyldiglycol carbonate-based track-etched detectors for the neutron dose measurements within the phantom. For the thermal neutron energy range, thermoluminescence detectors enriched with ^{6}Li were used. The proton beam was a spread out Bragg peak with a modulation of 10 cm from a pencil beam scanning beam line with a maximal energy of 170 MeV. They quantified the neutron dose and compared the results for the different types of detectors at each measurement position. Perpendicular to the primary beam, they reported neutron dose equivalents of ~700 and ~60 μSv/Gy at a distance of 10 and 30 cm from the center of the spread out Bragg peak, respectively. The results were also compared with data from the literature. The comparison with neutron dose measurements published by Hälg et al[15] showed that the results of both experiments were in the same order of magnitude, which may be considered as a good agreement between two independent data sets. By comparing their results to a very similar experiment with a single field irradiation using a 20 MV photon beam,[16] Stolarczyk et al found almost no difference in the measured neutron dose equivalents. On the other hand, the out-of-field secondary photon dose in proton spot scanning was up to three orders of magnitude lower than for photon radiation therapy using 6, 12, and 20 MV photon beams. This is in good agreement with previously published data,[15] therefore Stolarczyk et al concluded that the contribution to the total out-of-field dose by secondary neutrons in proton spot scanning is small.

In clinical proton therapy, there are two major techniques to produce the proton irradiation field to cover the lateral extension of the treatment volume. These techniques are passive scattering or active scanning of the proton beam. As there are more components of the beam delivery system in passive scattering proton therapy which directly interact with the primary beam than in active scanning, neutron doses in passive proton therapy are higher by design. A special proton beam delivery technique, which can be seen as a kind of mixture of both delivery systems, is a so called wobbling nozzle beam delivery system. It uses magnets to apply the wobbling to the primary protons, but it also uses a scatterer to widen the beam. Liao et al looked at a wobbling system, which consisted of wobbling magnets, a scatterer, ridge filter, fine degrader, dose monitor, flatness monitor, multileaf collimator, compensator, and patient aperture.[17] All these nozzle components are possible sources of secondary neutrons. It is therefore interesting to see, how the wobbling system compares to active scanning and double scattering in terms of neutron exposure. Liao et al measured their system using a WENDI-II detector to characterize the neutrons in terms of ambient dose equivalent and compared their findings to previously published data for other beam lines using wobbling,[18] double scattering,[18] or uniform scanning.[19] The detector was placed at different lateral distances from a solid water phantom, which was used to stop the primary beam with energies of 150 and 230 MeV. In addition, the influence of the primary beam energy, the field size, the width of the spread out Bragg peak, and the air gap on the neutron dose was investigated. Liao et al were able to confirm that the neutron ambient dose equivalent increases with the proton beam energy and the spread out Bragg peak width, as well as that it decreases with the distance from the isocenter. They showed a clear increase in the neutron ambient dose equivalent with increasing wobbling diameter size. The neutron dose from the medium wobbling diameter was 2.1 times larger than from the small diameter, whereas the large diameter was 3.3 times larger than the small one. Depending on the measurement conditions, they reported neutron ambient dose equivalents between 150 μSv to about $5{\cdot}10^{3}$ μSv per treatment Gray. Liao et al concluded that the measured neutron doses were similar to those of other facilities and the differences depend on the specific beam line design. They did not give a general conclusion, how wobbling systems compare to active and passive proton beam lines concerning neutron production.

For investigations of any kind of dose, measurements are the gold-standard. Despite the challenges in neutron dosimetry, it is also true for neutron dose studies. There has been a large number of publications involving neutron dose investigations in the last few years. This shows that it is still a topic of interest and the fact that more proton pencil beam facilities are being built, might be an indication that the scatter dose contribution of neutrons is not being neglected. The following Table 1 summarizes neutron dose measurements in proton therapy, which have been published recently. Some of the publications in the table have been mentioned above, but not all articles could be included in the discussion. If several measurement conditions for neutron dose were reported, only part of the results were included in the table. In Figures 1 and 2, the neutron doses from Table 1 are visualized for the angles 0° and 90° as a function of distance from isocenter. The different beam delivery systems are drawn as different symbols and a separation into low energy

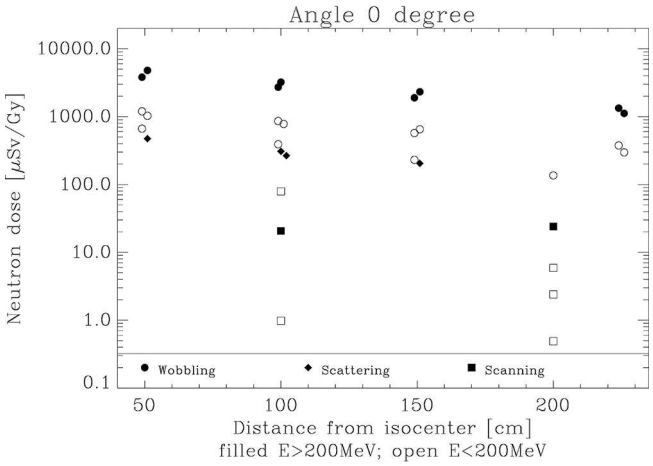
Table 1. Summary of neutron dose equivalent measurements per treatment dose from recently published literature

Author	Detector	Beam delivery	Energy /MeV	SOBP /cm	Distance /cm	Angle /°	Neutron Dose /μSv/Gy
Ciocca et al[20]	Bb	PBS	86	2.3	6.4	90	68
Han et al[21]	W-II	S	217.8	5	50, 100, 150	0	474, 308, 205
Islam et al[22]	ET	US	78, 162, 226	0	17.5	90	$1.24.10^3$, $4.05.10^3$, $6.64.10^3$
Lee et al[23]	WII	W	190	10	50, 100, 200	90	$1.38.10^3$, $1.03.10^3$, 512
	W-II	LS	190	10	50, 100, 200	90	20, 10, 5
	W-II	PBS	190	10	50, 100, 200	90	16, 9, 5
Liao et al[17]	W-II	W	150	6	50, 100, 150, 225	0	$1.03.10^3$, 781, 573, 297
	W-II	W	230	6	50, 100, 150, 225	0	$3.82.10^3$, $2.72.10^3$, $1.90.10^3$, $1.12.10^3$
	W-II	W	150	10	50, 100, 150, 225	0	$1.20.10^3$, 860, 652, 376
	W-II	W	230	10	50, 100, 150, 225	0	$4.80.10^3$, $3.22.10^3$, $2.32.10^3$, $1.33.10^3$
Lillhök et al[24]	TEPC	PBS	146	10	100	0, 45	79, 41
Lin et al[25]	W-II	W	190	0	50, 100, 150, 200	0	665, 391, 231, 136
Mojzeszek et al[26]	W-II	PBS	100	0	100, 150, 225, 225	0, 90, 270, 225	0.98, 0.89, 0.43, 0.49
	W-II	PBS	200	0	100, 150, 225, 225	0, 90, 270, 225	20.73, 5.91, 3.46, 2.22
Prusator et al[27]	W-II	S	250, 25 cm*	20	100	0, 45, 90, 135	266, 297, 358, 504
	W-II	S	250, 25 cm*	20	20, 40, 60, 80, 100, 150	90	501, 443, 389, 365, 357, 320
Stolarczyk et al[14]	ET	PBS	170	10	9, 14, 19, 24, 29, 34, 39	90	$1.73.10^3$, 770, 280, 130, 80, 50, 30
Trinkl et al[13]	BS	PBS	75	0	200	0, 45, 90, 135	0.49, 0.39, 0.26, 0.37
	BS	PBS	140	0	200	0, 45, 90, 135	5.9, 3.2, 1.6, 1.5
	BS	PBS	200	0	200	0, 45, 90, 135	24, 11, 5.3, 4.1
	BS	PBS	118, 5 cm RS	0	200	0, 45, 90, 135	2.4, 2.8, 1.2, 1.2

BS, Bonner sphere; Bb, Bubble detector; ET, Etch track detector; LS, Line scanning; PBS, Pencil beam scanning; RS, Range shifter; S, Scattering; TEPC, Tissue equivalent proportional counter; US, Uniform scanning; W, Wobbling; W-II, WENDI-II.

The given angle is relative to the proton beam direction. If several distances and angles are given in one row, each distance corresponds to one angle and one dose in the order it is listed. *Proton beam energy in MeV and actual range in cm.

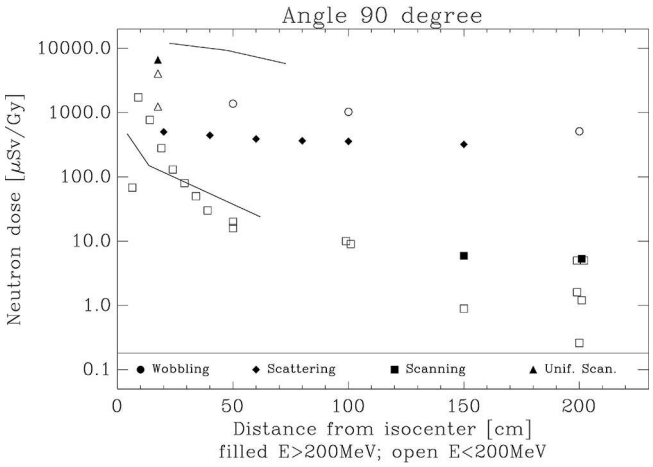
Figure 1. Neutron dose equivalent in μSv per treatment Gy as a function of distance from isocenter along the direction of the primary proton beam (Angle 0°) from the publications in Table 1. The different beam delivery systems are drawn as different symbols. Open and filled symbols show low or high energy proton beams. Experimental data points have been slightly shifted around their distance for better visibility.



(<200 MeV) and high energy (>200 MeV) is shown by open and filled symbols, respectively.

As discussed earlier in this section, neutron dosimetry is no straight forward task. Investigating neutrons in radiation therapy always means dealing with mixed fields. Neutron detectors therefore not only have to cover a wide energy range, but also the sensitivity to other types of radiation should be as low as possible. In radiation therapy, the goal of measurements, for instance neutron dose, is usually to quantify the radiation exposure for patients or for staff members. Especially in neutron dosimetry, *in-vivo* measurements are very challenging. And for obvious reasons, most research experiments cannot be performed with *in-vivo* measurements. Therefore, the patient is commonly replaced with a so called phantom. Common phantom materials are water- or tissue-equivalent plastics. Tissue equivalence is a very important point in this context. As the patient is replaced with phantom material, it is of utmost importance that the chosen material behaves like real tissue within measurement uncertainties. The International Commission on Radiation Units and Measurements defines tissue-equivalent material in their report 30[28] "A material, the absorption and scattering properties of which, for a given irradiation, simulate as nearly as possible those of a given biological material, such as soft tissue, muscle, bone or fat. Water is usually the best soft tissue-equivalent material for X and γ radiation." The property of tissue equivalence is widely used in radiation therapy, but the fact that it is dependent on the type of radiation, is rarely discussed. Most commercially available tissue-equivalent phantoms are made for photon irradiations. For neutron measurements in proton therapy, it is not a priori clear that a tissue- or water-equivalent phantom made for photon irradiations, also is a good substitute for tissue in a proton beam. Different phantom materials have been investigated for tissue-equivalence in regard to neutrons[29,30] and choosing the appropriate phantom material should be part of any investigation that includes neutron measurements. Different approaches have been taken to overcome these difficulties in neutron dosimetry and progress has been made in developing new means of estimating the true neutron dose in the last years. In this section, some of the new developments in the field of neutron detectors are presented. The group of Ytre-Hauge et al tried to overcome the disadvantages of passive detectors and the large physical size of active neutron detectors. They present a first application of a neutron detector based on registration of radiation induced effects in Static Random Access Memories in order to perform neutron measurements inside phantoms with a fast readout system.[31] The measurement device was placed in a water phantom and irradiated with a proton pencil beam of 178 MeV. A neutron energy response model was developed for the new system to increase the accuracy in the neutron energy range typical in proton therapy. This allowed to determine the internal neutrons from proton pencil beam scanning. To benchmark the new detector system, Monte Carlo simulations and measurements with thermoluminescence detectors were performed. They found that the detection threshold of 3 MeV of their new system is low enough to capture approximately 90% of the neutron dose in pencil beam scanning proton therapy. The investigated neutron spectra had a small impact on the detector response and they suggest the possibility of position-specific calibration factors. They conclude that the results demonstrate the potential for estimating spatial out-of-field neutron dose based on the Static Random Access Memory detector measurements in combination with the neutron energy response model.[31] The MONDO (MOnitor for Neutron Dose in hadrOntherapy) project is developing a neutron tracking detector.[32] It should be

Figure 2. Neutron dose equivalent in μSv per treatment Gy as a function of distance from isocenter perpendicular to the direction of the primary proton beam (Angle 90°) from the publications in Table 1. The different beam delivery systems are drawn as different symbols. Open and filled symbols show low or high energy proton beams. Experimental data points have been slightly shifted around their distance for better visibility. For comparison, minimum and maximum measured neutron doses for scattering proton therapy from the AAPM TG-158 report were added as solid lines.[6]AAPM, American Association of Physicists in Medicine.



able to investigate neutrons in the energy range of 20–400 MeV. By tracking recoil protons in a three-dimensional matrix of scintillating fibers, the system is able to determine flux, energy spectra, and angular distribution of the neutrons. The selection criteria for the recoil protons is two consecutive neutron elastic scattering interactions. The detector properties were optimized using Monte Carlo simulations and the findings presented in a publication. In addition, calibration and efficiency measurements were performed using a prototype detector in a clinical proton beam. Giacometti et al conclude that the experimental and simulation results are in good agreement. In the future, they want to include particle energy loss and timing information, to improve the detection capability of the MONDO tracker. Tagawa et al developed a novel neutron camera consisting of eight units of a plastic scintillator and a compact photomultiplier tube.[33] The camera can visualize neutron sources in real time and show their direction and intensity for applications in proton therapy. Neutron-induced recoil protons are registered and their energy is measured. Using a time of flight analysis, the energy of the incoming neutron is calculated. Using the information of the recoil proton and the neutron, the direction of the neutron source is determined. The time-of-flight information as well as pulse shape discrimination are used to distinguish between incoming photons and neutrons. In their publication, they showed that a ^{252}Cf neutron source could successfully be imaged with an angular resolution of 15.5° full width half maximum. A brass phantom was irradiated using a 70 MeV proton beam in two different positions relative to the neutron camera. The emitted neutrons were detected by the camera and the location of the brass phantom was successfully determined. In order to improve the neutron detection in a proton therapy environment, they increased the energy threshold to take advantage of the strongly reduced photon background above 10 MeV. A new Bayesian approach to get spectral information from neutron measurements using Bonner spheres was published by Dommert et al.[34] Typically, neutron spectrum information from Bonner sphere measurements is acquired using unfolding methods. The disadvantage of this procedure is the difficulty to get reliable estimates of uncertainties. The Bayesian approach is supposed to overcome this difficulty and improve the results of wide range neutron energy measurements, which only Bonner spheres are capable of. A new parameterized model was introduced to analyze stray neutrons in proton therapy. In order to build a parameterized model of the neutron spectrum, a superposition solution of a thermal peak, an intermediate region, a fast energy peak, and a high energy peak is necessary. The Bayesian analysis then requires a likelihood function and prior distributions for the parameters. The approach has been experimentally validated with measurements at an experimental beam line at a proton therapy facility. The neutron source was a brass target of simple geometry irradiated by the experimental horizontal proton beam of 224 MeV without a complicated therapy nozzle. The results of the Bayesian parameter estimation were in good agreement with established unfolding codes based on Monte Carlo calculated neutron spectra. The group of Chung et al looked into a neutron detector based on solid plastic scintillators, which can distinguish neutrons from photons.[35] They use a pulse shape analysis of the scintillation light for the particle discrimination. The specific plastic scintillator used, EJ299-33, has the potential to detect neutrons with energies up to 100 MeV and does not present leakage and flammability hazards generally associated with liquid scintillators. The group performed measurements with different radiation sources, namely ^{60}Co, ^{137}Cs, and ^{241}AmBe in order to calibrate the device. The measurement data were also used to optimize the pulse shape discrimination parameters. The device was also used to measure high energy neutrons produced by a passively scattered proton beam of 60 MeV. They were able to successfully register neutrons and photons, but they conclude that simulations are needed to further study the neutron energy calibration.

NEUTRON DOSE DISTRIBUTIONS AND THEIR CONSEQUENCES

Assessing the neutron dose distribution is not a straightforward task. There are different possible approaches and each has its own challenges and limitations. The gold-standard in any form of dosimetry is to perform measurements (see section Neutron Measurements and Detectors). Especially in neutron dosimetry, Monte Carlo-based simulations have been gaining importance. Analytical models to approximate the neutron dose distribution are usually based on measurements, Monte Carlo simulations, or both. Analytical models are developed for instance in order to integrate a neutron dose calculation into a treatment planning system or for research purposes.

In radiation therapy, neutrons are usually secondary particles produced by the interaction of primary beam particles with materials in the beam path. Therefore, in order to investigate neutrons, one has to deal with mixed radiation fields. This is part of the difficulties in neutron dosimetry, as an ideal detector, which only registers neutrons, is not available. In a computer simulation on the other hand, it is very well possible to separate the different constituents of a mixed radiation field. Monte Carlo simulation toolkits have been available for many years now, a lot of them tailored for particle transport in high energy physics applications. But these toolkits were not designed for such low energy applications, as are needed in medical physics. Only in recent years, the developers of these simulation packages have been aware of the needs for simulations in medical physics. Thanks to these developments and the advances in computer hardware, Monte Carlo simulations for radiation therapy purposes have become well established. Especially in proton therapy, or more general in particle therapy, Monte Carlo simulations play an important role, for instance for beam line design, shielding verification, patient dose calculation, and of course for secondary neutron investigations. In order to get precise results when performing Monte Carlo simulations, it is important to include as many details of the irradiation situation as possible. For neutron simulations, it is especially important to include the beam modifying devices in the treatment nozzle. Trinkl et al[13] identified the nozzle components and their materials as the most important sources of neutrons in proton therapy. It is therefore absolutely necessary to include these parts with as much details as possible in any simulation where neutrons are involved.

In a study by Prusator et al, Monte Carlo simulations of neutron dose were reported and benchmarked with measurements carried out using a WENDI-II detector for a passive scattering proton therapy system.[27] The goal of the work was to verify the shielding of the MEVION S250 proton system, which is mounted on a rotating gantry inside the treatment room. This single room design is specifically challenging for radiation shielding, both concerning the patient and the staff. They used several neutron sources in their Monte Carlo simulation setup to account for the neutron contribution from the cyclotron, the beam delivery nozzle, and the patient. The patient was represented by a cubic water phantom. The concrete vault was included in the simulation geometry, which is essential for shielding investigations, but also for in-room neutron studies, as neutrons bounce back from the walls. The proton beam used for the shielding simulations had an energy of 250 MeV with a range between 15 and 30 cm and modulation width between 10 and 20 cm. The angular dependence of neutron fluences and energy spectra were simulated and neutron ambient dose equivalent per incident proton was calculated using fluence to dose conversion factors. They found that the cyclotron had the largest neutron contribution, followed by the nozzle, and the water phantom. The largest neutron doses were found in the direction of the primary proton beam and for the smallest field sizes. The comparison of the simulation and the measurement showed the same trends in all measurement locations, but the simulation results were about an order of magnitude higher than the measurements. As an explanation for this difference, they suspect the neutron point source model of the cyclotron to be too simplistic.

The influence of field arrangement in proton pencil beam scanning radiation therapy on organ doses from secondary radiation was investigated in a recent paper.[36] Treatment plans using a single lateral or vertex field were created for an adult female and a pediatric patient. The involved proton beam energies ranged from 80 to 126 MeV. Whole body CT scans of the patients with 15 delineated organs at risk and target volumes were included in the Monte Carlo model. The simulation scored absorbed dose and neutron equivalent dose was calculated using the radiation weighting factors from report 103 by the International Commission on Radiological Protection. Additionally, the neutron energy fluence spectra were scored in the included organs at risk. The organ absorbed doses were reported as the sum of all secondary particles. Only the neutron equivalent dose was reported separately. Ardenfors et al concluded that the doses from secondary particles in proton pencil beam scanning for brain tumors are relatively low and in the order of mSv. In general, the organ doses for the pediatric patient were higher compared to the adult patient, but the differences were small in absolute terms. For the field arrangement, they found that the vertex field caused higher organ doses in most organs at risk, but the variations were small as well. They therefore say that the field arrangement does not lead to large variations in the out-of-field dose for proton pencil beam patients.

Proton pencil beams with primary energies of 70, 150, and 200 MeV were investigated in a paper by Yeo et al to quantify the spatial and angular distribution of secondary neutrons.[37] The proton beams were impinging on phantoms made of 24 different materials with dimensions $30 \times 30 \times 30\,cm^3$. For the secondary neutrons, only the production was simulated and the energy, momentum, and position of production were scored. No transport of the neutrons in the phantom materials was simulated. A lethality factor was defined as the track-summed RBE of the neutrons in each voxel to quantify the maximum risk of localized DNA damage from neutrons at production.[37] The RBE values used for this assessment were taken from another publication.[38] In that study, Baiocco et al combined neutron transport simulations using Monte Carlo with biophysical track structure calculations to evaluate DNA damage. Extensive calculations of neutron-induced secondary charged particles, their contribution to the total neutron dose, as well as neutron energy and location dependent lineal energy were performed to evaluate neutron RBE based on dose-mean lineal energy and DNA double strand break cluster induction. Yeo et al summarize their findings that most of the neutrons produced in any of the tissue phantoms have an energy below 1 MeV and are predominantly forward directed. The forward direction is more pronounced for higher beam energies. Neutrons in this intermediate energy range have a high RBE and they conclude that these can result in a high localized damage. They also say that the proton beams in treatment planning should not be directed towards dense structures like cortical bone, because these showed the highest lethality factors in their study. In practical terms, this means that if two proton treatment plans have the same tumor control probability and the normal tissue complication probability is very similar too, the treatment plan that better avoids dense structures, should be preferred.

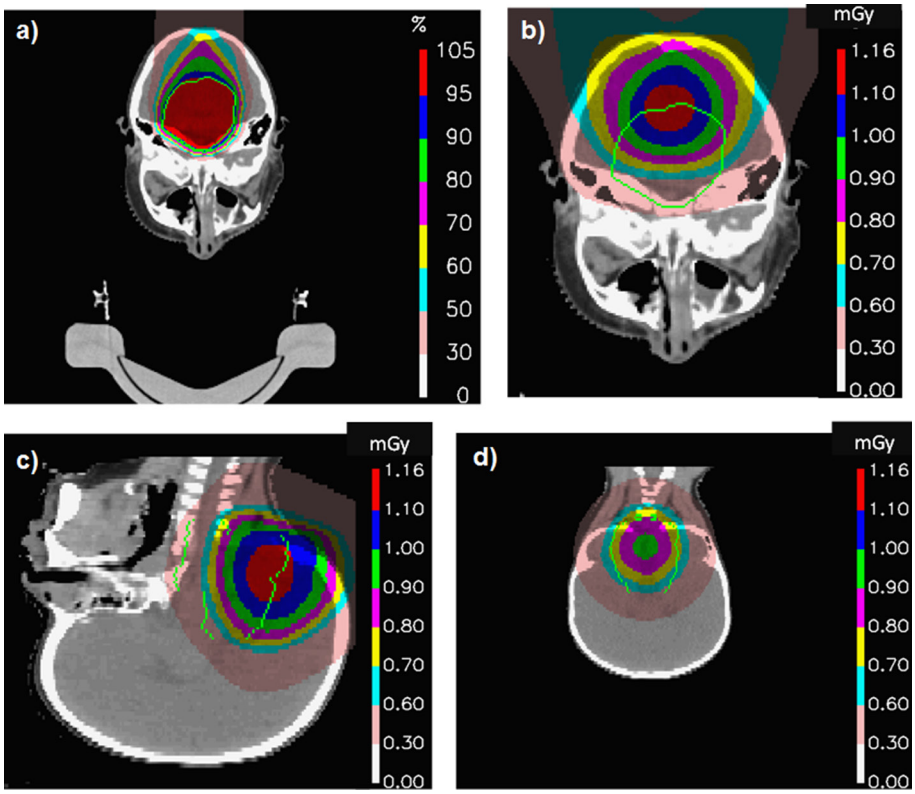
Monte Carlo simulations were also used to investigate a wobbling proton beam delivery system (see also section Neutron Measurements and Detectors) concerning the neutron production.[25] Lin et al used a WENDI-II detector to benchmark their simulations. The Monte Carlo model contained all the major beam delivery devices: vacuum window, profile monitor, beam dose monitor, fine degrader, snout, aperture, multileaf collimator, and a range compensator. Specifically for the wobbling system, it also contained two dipole wobbler magnets, a scatterer, and a ridge filter. The investigated proton beam energy was 190 MeV. The ridge filter was set to produce a 10 cm spread out Bragg peak. Neutron fluences were scored at different locations with distances up to 200 cm from the isocenter and with angles of 0, 45, and 90° relative to the primary beam direction. The simulated neutron fluences were converted to neutron ambient dose equivalent and neutron dose equivalent using conversion coefficients from literature. The calculation and measurement of neutron ambient dose equivalent along the lateral direction showed good agreement. They were able to identify a larger number of high energy neutrons in the forward direction of the proton beam, which were produced by the intranuclear cascade. The largest number of neutrons around 1 MeV coming from the evaporation process were found at an angle of 90°. Like Liao et al.[17] (see section Neutron Measurements and Detectors), Lin et al were able to confirm that the neutron dose decreased with increasing distance from the isocenter. In addition, they found that the neutron dose generally increased with an increase in the angle

relative to the proton beam. At 90° angle, they found a difference in the neutron dose depending on the direction relative to the multileaf collimator. In the direction of the movement of the multileaf collimator, the neutron dose was found to be lower. Lin et al conclude that care should be taken with the positioning of the patient, if the patient axis is at a 90° angle of the proton beam, because of the shielding effect of the multileaf collimator. In addition, they say that the neutron dose level in their study was lower than that of passive scattering nozzles, but higher than that of a pencil beam scanning system.[25]

Measurements and in particular Monte Carlo simulations can give detailed insights into an investigated topic. Therefore, they are the preferred methods for neutron dose determination. The downside is that they are time and resource intensive.[39,40] Commercial solutions for Monte Carlo simulations in radiation therapy are sparsely available and they are usually tailored to a specific task. And even with commercial tools, full Monte Carlo simulations are still very time consuming. Analytical models can fill this gap. They can be precise enough for routine tasks in the clinic and treatment planning. The time needed to perform the calculations can be in the order of minutes, which is acceptable even for daily tasks. Using an analytical model for whole body stray dose calculations, for instance the neutron dose from proton beams, can facilitate the comparison of different clinical proton treatment plans. Consequently, not only the conformality of the primary dose to the target volume calculated by the treatment planning system can be compared, but also the amount of neutron dose to distant organs at risk can be evaluated in the treatment planning process. This would be a further step in trying to minimize treatment-related late effects. Newhauser et al published a review in 2018 on analytical models of stray radiation exposures.[41] They looked into stray doses from proton and photon beam radiation therapy. For proton therapy, they distinguished three categories of analytical models: collimator scattered protons, external neutrons, and internal neutrons. For stray dose investigations, only the neutron models are of interest, as collimator scattered protons do not contribute to the stray dose away from the target volume. External neutrons refer to neutrons produced in the proton beam nozzle by nuclear interactions of the primary protons with the beam forming devices, whereas internal neutrons refer to neutrons produced by nuclear interactions within the patient. In active proton therapy, for instance using proton pencil beam scanning, only models for internal neutrons are needed, as only very few neutrons are produced in the beam line components. On the other hand in passive proton therapy, *e.g.* double proton scattering beam lines, models for external and internal neutrons are needed, because the primary proton beam interacts with components in the nozzle, such as the scatterers and the field specific aperture, and with the patient's body. Therefore, the neutron stray dose from passively scattered proton treatments is intrinsically higher compared to scanned-beam techniques, which has been shown by measurements and Monte Carlo simulations in the past. In the last 2 years, two new analytical models for neutron dose in proton therapy were developed. Schneider et al integrated neutron absorbed dose and neutron dose equivalent dose kernels for pencil beam scanning into the treatment planning system at Paul Scherrer Institut.[42] The kernels were generated using a full Monte Carlo model of their pencil beam scanning gantry with proton beams impinging on a water phantom. The results for the proton dose calculation and the neutron dose estimation for two patient cases can be found in Figure 3 (ependymoma) and in Figure 4 (cranio-spinal). In another publication, an extension of the model for neutron energy, quality factor, and RBE was introduced.[43] Gallagher and Taddei used the model for external neutrons from Schneider et al[44] and modified it to apply it in a clinically realistic environment.[45] They adjusted the model to account for the treatment field parameters of two pediatric patients and compared the calculations to previously published Monte Carlo simulations. They found that the accuracy of the adjusted model to be sufficient for the purpose of estimating the risks of radiogenic cancers and that they were able to reproduce the neutron stray dose results from full scale Monte Carlo simulations within a factor of two.[45] In a follow-up paper, Gallagher and Taddei extended their model for external neutrons to internal neutrons using measurements and Monte Carlo simulations to determine equivalent dose.[46] In their review article, Newhauser et al concluded that rapid progress has been made in the last few years toward understanding the systematics of how stray exposures depend on a myriad of treatment factors and that it was demonstrated that it could be possible to prospectively calculate stray doses on a routine basis within about 5 years.[41] The work published in the last 2 years about modelling neutron doses in proton therapy has shown that this trend is continuing.

To cover a target volume with dose in proton therapy, proton beams with many different energies are needed. A common technique to transform the small number of distinct primary proton energies from the accelerator into many therapeutic proton energies is called range modulation. This has traditionally been done by a range modulator wheel or by range-shifter plates in the treatment nozzle. More recent proton beam delivery systems try to avoid the need of these devices and perform different methods of energy selection, or place them upstream outside of the treatment room, so the secondary neutrons from this process can be shielded.[47] The range modulation devices change the proton energy by varying the amount of material traversed by the protons before impinging on the patient. This beam forming device is one of the possible neutron sources inside the proton nozzle. Trinkl et al[13] compared two proton beams with and without range modulation, both with similar ranges. A range-shifter of 5 cm inside the treatment nozzle increased the neutron dose 45° in relation to the primary beam by a factor of 7.2 for the beam of 118 MeV compared to the non-modulated beam of 75 MeV. To optimize a treatment plan in proton therapy in terms of neutron dose, it is therefore important to minimize the use of range modulation. Not only the amount of range modulation, which has to be applied, also the primary proton energy has a direct influence on the neutron dose. Trinkl et al[13] also showed that the neutron dose increases with the proton beam energy. They observed a maximal increase by a factor of 50 in neutron ambient dose equivalent for the maximal energy of 200 MeV compared to the lowest energy of 75 MeV in beam direction behind the phantom.

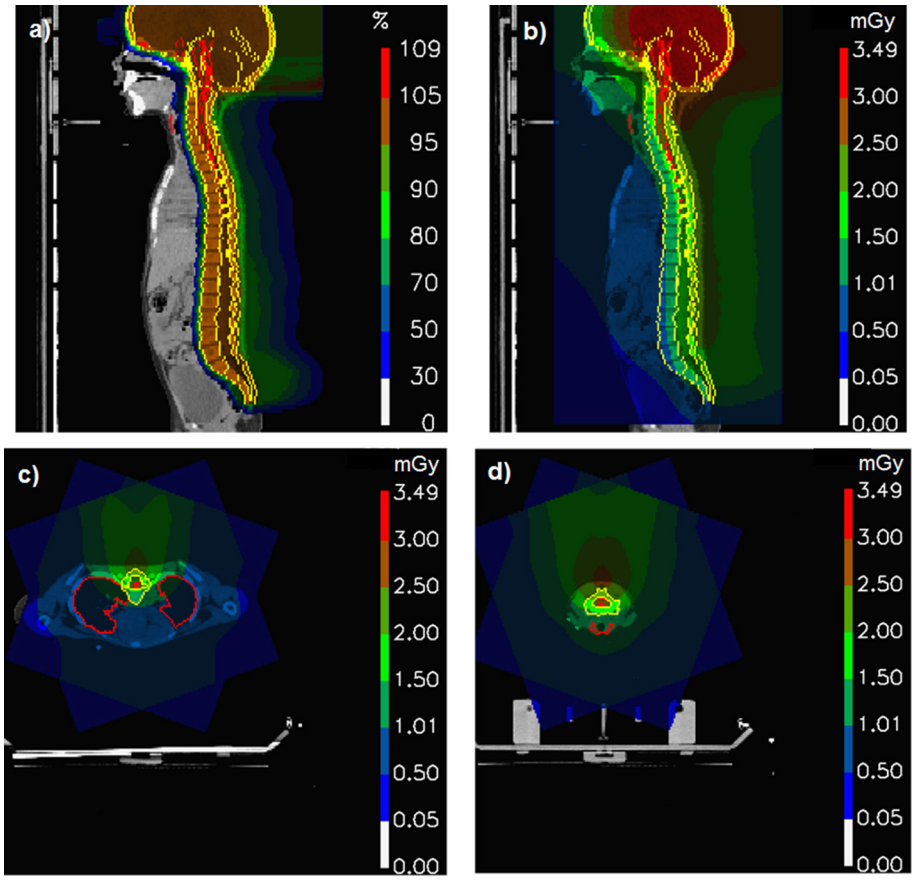
Figure 3. Proton dose distribution for the pediatric ependymoma (Case 1) planned with 160 MeV protons in (a). The corresponding neutron dose distributions in mGy per fraction are shown in (b–d). From Schneider et al.[42]



In order to increase the dose conformity to the target volume, different beam shaping devices have been developed and tested in proton therapy over the years. It has been shown for instance for proton pencil beam scanning, that a Dynamic Collimation System (DCS) can provide superior target conformity and healthy tissue sparing when compared with conventional pencil beam scanning treatment modalities.[48–50] But every additional component in the proton treatment nozzle is a potential source of secondary neutrons. Therefore, not only the effect on dose conformity should be evaluated, but also the amount of secondary neutron production. A current approach was investigated by Smith et al[51] for intracranial pencil beam scanning proton therapy. They used Monte Carlo simulations to characterize a DCS based on trimmer blades. Single-field uniform dose and intensity-modulated proton beams for a dual-field chordoma treatment plan with and without dynamic collimation were compared. They reported a median healthy-brain neutron ambient dose equivalent using the DCS of 970 μSv/Gy for the right lateral and $1.37{\cdot}10^3$ μSv/Gy for the apex single-field uniform dose. Without the DCS, the neutron dose was reduced by about a factor of 2 to 570 μSv/Gy and 670 μSv/Gy, respectively. For the intensity-modulated proton plan, a total of $1.24{\cdot}10^3$ μSv/Gy was found using DCS and 710 μSv/Gy without DCS, again a substantial reduction. The group of Smith et al also looked at excess relative risk and lifetime attributed risk. Although the relative increase in neutron dose and excess relative risk with the application of this specific DCS is large, they conclude that the lifetime attributed risk from this neutron exposition is minimal and that the reduction in acute side-effects due to the improved conformity far outweighs the additional risk from the produced neutrons.

Reducing radiation induced late effects while keeping the tumor control rates high, is a current topic of interest in radiation oncology. With a growing number of long-term cancer survivors, it is more and more important to have a better understanding of the risk of cancer induction by ionizing radiation. As mentioned earlier, this is especially important for pediatric patients. In case of proton therapy, radiation-induced second cancer can occur from any of the radiation types in the mixed field. Because of the large uncertainty in the radiation weighting factors of neutrons, the focus of many second cancer studies is on the dose from secondary neutrons. A study on human breast cells was published in 2017 where different radiation qualities, including neutrons, were investigated. Juerß et al irradiated MCF10A cells with doses up to 2 Gy with broad energy spectrum neutrons ($<E_n>$=5.8 MeV), monoenergetic neutrons (1.2 MeV, 0.56 MeV), and with a mixed field of photons and neutrons ($<E_n>$=70.5 MeV) produced by a 190 MeV proton pencil beam impinging on a water phantom.[52] Radiation-induced DNA double-strand breaks and the clonogenic survival were determined after irradiation. Using X-rays as a reference (220 kV, 1 mm Al, 0.25 mm Cu, 0.45 mm Sn filter), the observed radiation effects of neutrons were compared using the concept of RBE.[52] Also two different dose rates were investigated. Monte Carlo calculations were performed to determine the neutron spectra in the liquid cell suspensions and to account for scattered neutrons in the sample holder. The determined RBE values

Figure 4. Proton dose distribution of the cranio-spinal irradiation (Case 2) shown in (a). The corresponding estimated neutron dose distributions in mGy per fraction are shown in (b–d), with figure (c) showing the neutron dose at the level of the breast and figure (d) at the level of the thyroid. From Schneider et al.[42]



based on clonogenic survival after irradiation were 4.97 and 3.75 (monoenergetic neutrons 0.56 and 1.2 MeV), 2.09 (mixed photon neutron field), and 2.06 and 1.99 for high and low dose rate (broad energy spectrum neutrons), respectively. Double-strand break-based RBE values were 7.95 and 3.98 (monoenergetic neutrons 0.56 and 1.2 MeV), 4.47 (mixed photon neutron field), and 4.57 and 5.25 for high and low dose rate (broad energy spectrum neutrons), respectively. They conclude that the RBE values are coherently increasing for decreasing neutron energy in the investigated energy range. The exposure to the mixed photon—secondary neutron field yield RBE values as high as for medium-energy neutrons.[52]

The concept of weighting the energy deposition in tissue by neutrons is based on physical and biological properties. For instance, the particle energy as the physical property and the biological context would be, *e.g.* the investigated end point. The group of Imaoka et al looked into age as a biological factor for neutron RBE determination.[53] From the perspective of radiological protection, age is an important aspect, which influences radiation-related cancer risk. Their goal was to investigate the age effect for neutrons, because very few studies have addressed this so far. Imaoka et al therefore investigated the influence of age on the effect of accelerator-generated fast neutrons (mean energy about 2 MeV) in an animal model of breast carcinogenesis. Female Sprague-Dawley rats at 1, 3, and 7 weeks of age were irradiated with fast neutrons at absorbed doses of 0.0485–0.97 Gy. All animals were kept under specific pathogen-free conditions and screened weekly for mammary tumors by palpation until they were 90 weeks old. Tumors were diagnosed based on histology. Mathematical modeling was used to analyze mammary cancer incidence, collectively using data from this study and a previously reported experiment on a ^{137}Cs photon beam. They found that the results indicate that neutron irradiation elevated the risk of palpable mammary carcinoma with a linear dose response, the slope of which depended on age at time of irradiation. The RBE of neutron radiation was 7.5 ± 3.4, 9.3 ± 3.5 and 26.1 ± 8.9 (mean ± SE) for animals exposed at 1, 3, and 7 weeks of age, respectively. These results indicate that age of the animal is an important factor influencing the effect of fast neutrons on breast cancer risk.[53]

A more general article about second cancer risk after particle therapy was published by K. R. Trott.[54] He discusses the radiobiology of the unwanted effects of radiation therapy, the dependence of radiation-induced second cancers on exposed organ, dose, dose distribution, age, and gender, the variable LET along the particle track and the RBE of secondary neutrons, as well as the ANDANTE project,[55] which investigated the relative risk of induction of cancer from exposure to neutrons compared

to photons. Trott elaborates that the absolute risk of radiation-induced second cancer is in the order of 1% for adult patients who were treated with methods which caused relatively high out-of-field doses. It is generally accepted that proton therapy has smaller out-of-field doses. Therefore, Trott states that it is very unlikely that patients treated with highly conformal particle therapy are at a higher risk for radiation-induced second cancer than those patients treated with photons, whichever reasonable RBE is chosen. He adds that most of these patients will have a higher second cancer risk than those who were treated 20 or more years ago, but this will be due to their longer life expectancy because they were cured. For childhood cancer patients, Trott sees reasons for concern, because there is still a potential risk of second cancer from stray doses in proton therapy. But he also writes that although the possible undesired consequences for children are more complex and manifold than in adult patients, they will benefit from the better focusing of the radiation dose in the target by particle radiation therapy. He concludes that this benefit may far outweigh the still hypothetical second cancer risk from neutrons produced by particle beams in pediatric radiotherapy.

CONCLUSIONS

The stray dose contribution from neutrons in proton therapy is still being investigated by several research groups. Since 2016, the biggest reported progress has been in the field of neutron detector development. Several promising new neutron detectors are being developed and it will be interesting to see, how they will change the reporting of neutron doses in proton therapy. For now, performing neutron measurements stays challenging. Also more studies have been published since 2016 where neutron doses were either measured or simulated, but no clear new insights were reported. The comparison of neutron measurements from different studies is not a straightforward task. Many factors affect the results of neutron studies, as for instance the measurement setup, beam line design, or neutron detectors to just name a few. This leads to large differences in the reported neutron doses and therefore, drawing specific conclusions is difficult. Nevertheless, recent studies in this field were able to confirm earlier findings about the neutron dose exposure of proton therapy patients. The largest difference in neutron dose comes from different treatment techniques and therefore from different proton beam line designs. The used technique can alter the neutron dose in the order of magnitudes, whereas other factors have a smaller impact. This difference is getting less important with new proton therapy facilities, as mostly beam scanning nozzles are being installed nowadays. Still, it can be seen that higher proton beam energies clearly lead to higher neutron doses and the neutron dose is higher closer to the primary proton beam. It has been confirmed, that in comparison to the total stray doses in photon therapy, the out-of-field neutron dose in proton pencil beam scanning is relatively small. Concerning the biological effectiveness of neutrons, recent studies have not provided many new insights, but were able to confirm that the energy range around 1 MeV seems to be the most effective one. It has also been shown that this energy range is the dominant one for neutrons in the mixed field of stray radiation in proton therapy.

Analytical models of neutron exposure from proton treatment plans have made a lot of progress. Now, different analytical models for active and passive proton delivery systems exist. Additionally, it has been shown that they can be integrated into treatment planning systems to efficiently predict the three-dimensional neutron dose distribution in the patient. This does open up the possibility to include in the future, beside the proton dose distribution, also the neutron dose in the process of finding the best treatment plan for a patient in proton therapy.

In general, the publications in the last few years reported low neutron doses, especially in proton pencil beam scanning therapy. Together with the current knowledge about neutron RBE, it is therefore likely that the neutron dose has a small impact on the induction of second primary cancers for proton therapy patients. Even more, a reduction in second cancer risk for active and passive proton therapy is predicted by current models when compared to photon treatments. This is also in general agreement with current epidemiological results. It is therefore especially unlikely that an increase in second cancer rates will be observed from contemporary proton therapy, compared to the patients who have been treated with different radiation modalities within the past 20 years.

In order to properly assess the risk of second primary cancer from neutron exposures, two requirements must be met. Firstly, the input to the risk models, the neutron doses, must be as precise as possible. Ideally, organ specific absorbed doses are used as input to cancer risk assessments. These data are still mostly missing and remains a topic, which needs to be investigated more. Only accurate neutron doses can lead to improved risk estimates, independent of the precision of the risk models. Over simplified or incomplete dose estimates must not be used to calculate cancer risk for patients in radiation therapy. Monte Carlo simulations and realistic computational phantoms will continue to be a very valuable tool for this task. One of the big advantages is the possibility to directly evaluate the neutron fluence as a function of energy, which is linked to the biological effectiveness of neutrons. Secondly, the biological effectiveness of neutrons for the investigated endpoint needs to be known for risk models to successfully predict the cancer risk. Currently, the uncertainties are still too high and it is therefore necessary to gain more knowledge on the RBE of neutrons with regard to cancer induction. Future studies will have to further investigate the dependence of the neutron RBE on neutron dose, energy, dose rate, biological tissue, size, and age of the patient.

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